

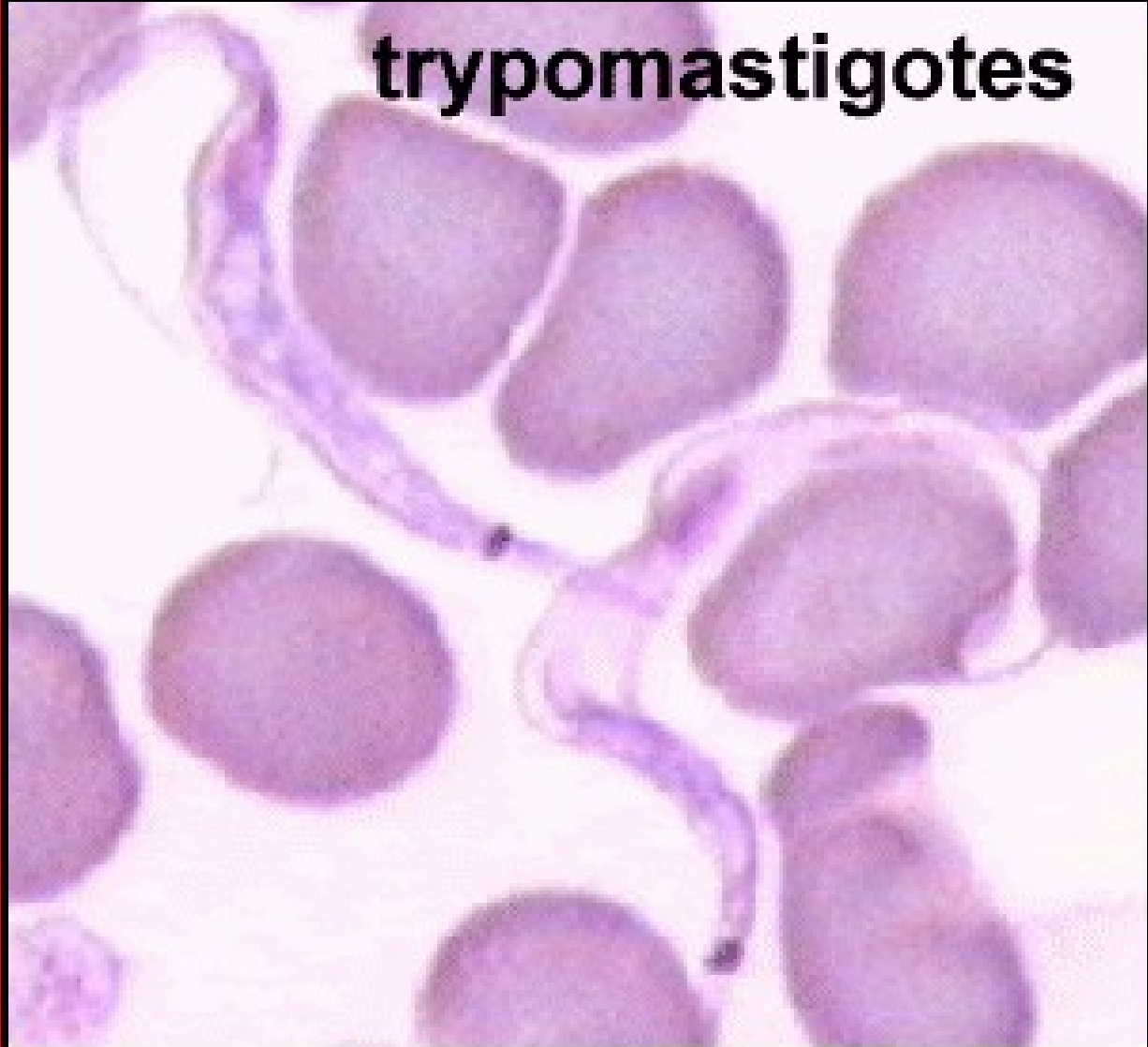
Measles, Meningitis, Diphtheria

Global Medicine Course 2005

Cap Nicholas G. Conger, MC, USAF

Fellow, Infectious Disease
Wilford Hall Medical Center

trypomastigotes



Case Presentation



Measles: Basic Characteristics

- Also known as rubeola
- Acute viral illness
- Primarily affects children
- Highly contagious
- Paramyxovirus
 - RNA, single stranded
- Vaccine preventable
 - Potential to be eliminated

Measles: Epidemiology

- 1990's: Present in all countries
 - 1995: 44 million cases
 - 1/3 of children born worldwide
 - 1.1 million deaths for children <5
- WHO focused on measles in 1990's
 - Current goal: decrease cases by 90% and mortality by 95%
- Currently: 1-2 million cases reported yearly
 - Thought to be gross underestimation
 - Most countries require reporting
- 800,000 deaths worldwide annually

Measles: Epidemiology

- Seasonal
 - Peaks in late winter or spring
 - Tropical countries: dry, cool season
- Males and females affected equally

Measles: Epidemiology

- Pre-Vaccine

- Epidemics
- Every 1-3 years
- Age: 3-15 months
- More frequent epidemics = younger age = urban > rural
- Importation to remote, naïve population can be devastating

- Post-Vaccine

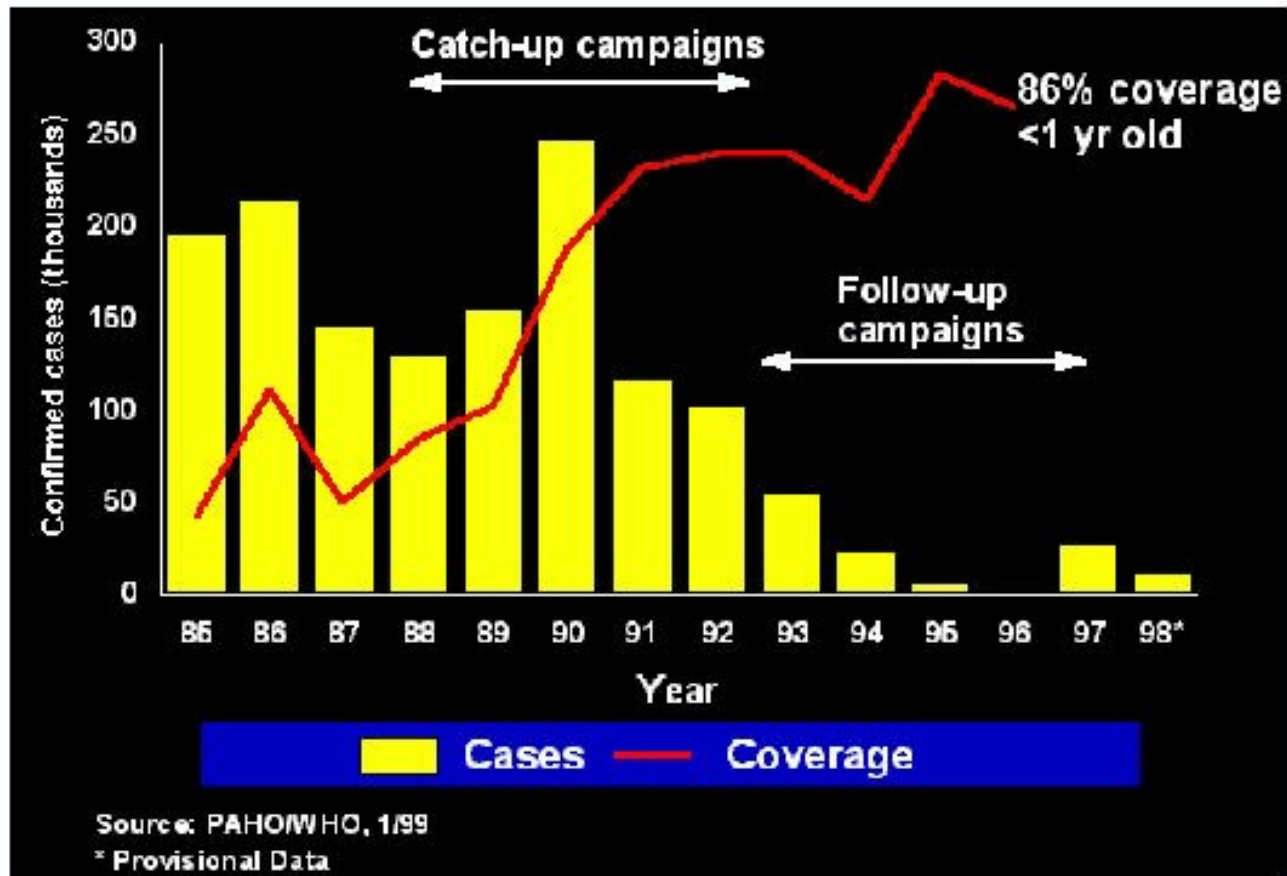
- Small epidemics
- Every 5-10 years
- Age of onset = older
 - Adolescents, young adults with 1 vaccine
- Majority of cases may be in vaccinated patients
- Cause: accumulation of unvaccinated population

Measles: Geographic Distribution

- Western Hemisphere and most of Europe
 - Vaccine strategies (2 shots) have interrupted transmission
- Middle East, Arabian Peninsula
 - Decreasing #'s with vaccination campaigns
- Africa
 - Poor control; most of the 800,000 deaths

Measles: Distribution

Reported Measles Cases Region of the Americas, 1980 - 1998

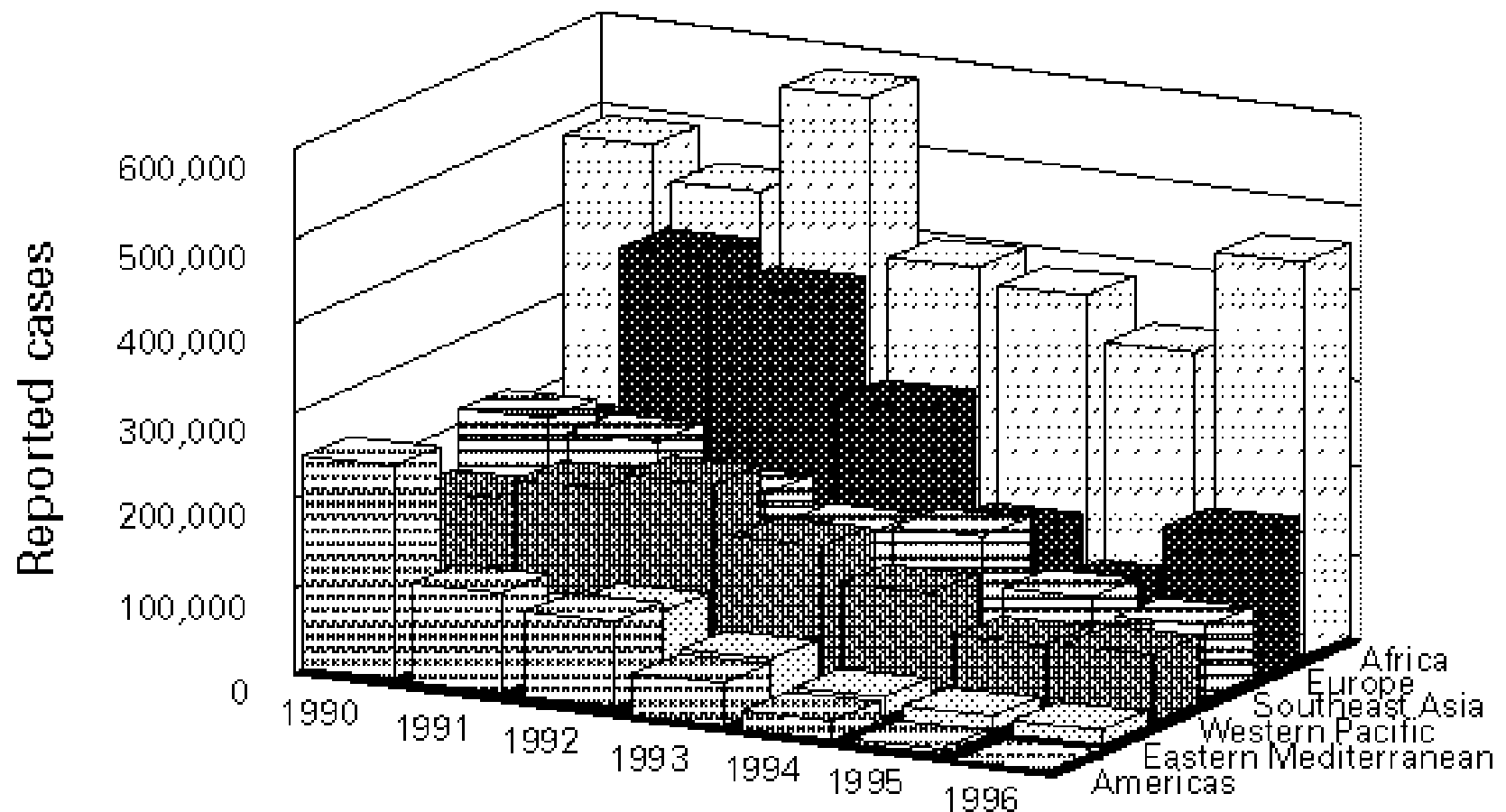


Measles: Distribution / US

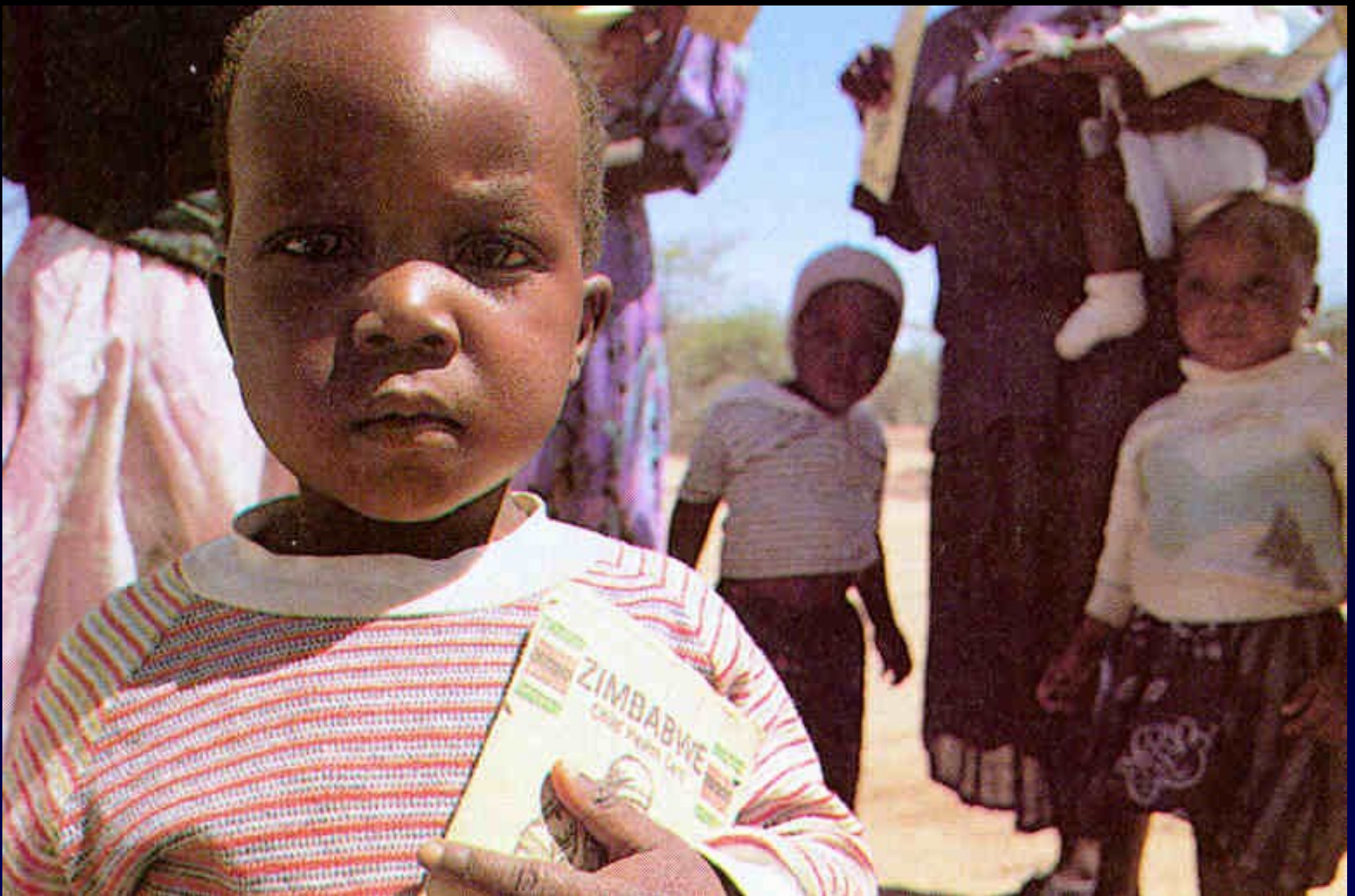
- 1997-2001
 - US case range: 86-138
 - Imported cases 26%-47%
 - 3-6% in US citizens that travel abroad
 - Internationally adopted children
 - Average - 2%
 - 2001 - 20% (10/11 associated with China)
 - US Law: all requesting visa's have to have at least 1st shot in every series

Measles: Distribution

FIGURE 2. Reported measles incidence by WHO* regions, 1990–1996



*World Health Organization



**Measles causes 800 000 deaths each year
worldwide-500 000 of them are in Africa**

Cutts: BMJ, Volume 316(7133).March 7, 1998.765-767

Measles: Transmission

- Person to person transmission
 - Humans are only reservoir
 - Droplet nuclei or aerosols
- Highly contagious
 - 90% attack rate for close contacts
 - In MD office – transmitted 2 hours later
- Patients are contagious for 7-10 days
 - Begins with onset of symptoms
 - Includes 2-4 day prodrome before the rash

Measles: Signs and Symptoms

- Incubation period: 10-12 days (8-16 range)
- Prodrome
 - Cough
 - NP, worsens over 4 days, then improves
 - Lasts through entire illness (7-10 days)
 - Conjunctivitis (purulent), coryza
 - May include photophobia
 - Lasts 6-8 days
 - Fever: 38-40° C: subsides after 1 week
 - Diarrhea
 - Chronic, serious if previously malnourished
 - State of prolonged virus shedding

Measles: Signs and Symptoms



- Koplik's spots
 - Part of prodrome: day 1-3 before rash
 - Raised papules on buccal mucosa and conjunctiva
 - Usually adjacent to molars
 - Often white on red base
 - Disappear about time rash occurs

Rash



**Measles:
Signs and
Symptoms**





Rash

Measles: Signs and Symptoms

Rash

**Hairline
Behind Ears**

Face

Trunk

Limbs



- Erythematous papular eruption
- Travels inferior over 2-3 days
- Coalesces into macular “splotches”
- Often desquamates at end of illness

Measles: Signs and Symptoms

- Peak of Illness
 - 2-4 days after onset of rash
- Other signs and symptoms
 - Anorexia, malaise, LAD, HSM
- Resolution
 - Rapid improvement at end of febrile period (1 week)
 - Complete recovery in 10-14 days
- Pearl: darker-skinned children
 - Sandpaper feel to rash may be helpful

Major Complications

- Acute Post-infectious Encephalitis
 - Occurs in 1-4/1000, 2-6 days after rash
 - Mild to fulminant (death in 24 hours)
 - 25% morbidity; 15% mortality
- Subacute Sclerosing Panencephalitis–SSPE
 - 2-15 years after infection
 - Progressive behavioral changes
- Secondary infections
- Myocarditis

Measles: Diagnosis / Clinical

- Clusters of children with fever, cough, conjunctivitis, coryza, morbilliform rash
- Koplik's spots can be classic, but easily missed



Measles: Diagnosis / Lab

- IgM serum antibody after onset of rash
 - Only single test; no acute / convalescent
- UK: RIA for IgM in oral secretions
- Acute and Convalescent sera
 - EIA or HIA – need samples 4-6 wks apart
- Virus isolation
 - Can even compare virus genomes
 - Expensive and at reference labs
 - Only way to distinguish infection from vaccine

Measles: Differential Diagnosis



Measles: Prognosis

- Mortality varies by age / nutritional status
 - Historically 1-5%
 - Higher with close contact secondary cases from presumed high viral exposure
 - US from '89-'91: mortality = 3/1000
 - West Africa/Asia: 25%
 - Death: pneumonia, malnutrition, diarrhea
- Risk factors
 - Immune compromise, Vitamin A deficiency
- Delayed excess mortality
 - Higher rates of death from other causes after measles infection in developing world

Measles: Treatment

- Supportive Care
 - Rest, hydration, nutrition, prn meds
 - Look for and treat bacterial super-infections
 - Rinse eyes daily (saline or sterile water)
- Vitamin A
 - May decrease mortality by 40%
 - Benefit may be independent of deficiency
 - WHO recs for both hospitalized and less ill
- Ribavirin
 - Inhibits viral replication in cell culture
 - Limited benefit in immune compromised patients
 - High cost makes = impractical in developing world

Measles: Treatment*

Vit-A → Age↓	Initial Dose	Final Dose 2 weeks later
0 - 5 Months	50,000 IU / day X 2 days	50,000 IU
6 - 11 Months	100,000 IU / day X 2 days	100,000 IU
>12 Months	200,000 IU / day X 2 days	200,000 IU

***WHO Recommendations**

Measles: Prevention

- Maternal antibodies
 - Protect for 3-12 months; usually 6 months
 - Presence of Ab's makes vaccine less effective
- Passive Immunization
 - Gamma globulin (0.25mg/kg)
 - For: high risk pts and exposure within 6 days
 - Pregnant, immune suppressed, children too young for vaccine, active TB, leukemia, known HIV
 - Impractical for developing world

Measles: Prevention

- Vaccine Immunization
 - Live attenuated vaccine
 - Usually given with MMR (2 doses)
 - US: 12-15 months; 2nd at 4-6 years
 - Efficacy (seroconversion)
 - Lifelong immunity
 - 9 months: 80-85% (used in developing countries)
 - >12 months: 95% (used in developed world)
 - Contraindications (live vaccine)
 - Immune suppressed, leukemia, lymphoma, pregnancy, anaphylaxis to neomycin or gelatin
 - Most recommend vaccinating HIV patients

Measles: Prevention

- Vitamin A
 - Recommended at regular intervals (3-6 months) in developing countries
 - Targets children ≥ 6 months old
 - Decrease mortality by improving nutrition
 - Benefit likely involves many infections, but measles is at the top



Measles: Mission Impact



**Bhutanese Refugee Camp
Jahpa, Nepal. Dec. 97
Photo by Moshe Cohen**

- One of the first disease that can wreak havoc on displaced populations
 - War torn areas
 - Refugee camps
- Preventable
 - Vitamin A can be given immediately
 - One of first vaccinations to consider

Measles: Summary

- Distribution: worldwide; worst in Africa
- Clinical Disease
 - Prodrome, Koplik's spots, morbilliform rash
- Treatment: supportive and Vitamin A
- Diagnosis: clinical, IgM serum antibody
- Prevention: Vitamin A, Vaccine
- Mission Impact:
 - Devastating disease of refugees
 - Priority when giving aide to displaced people

Case Presentation n

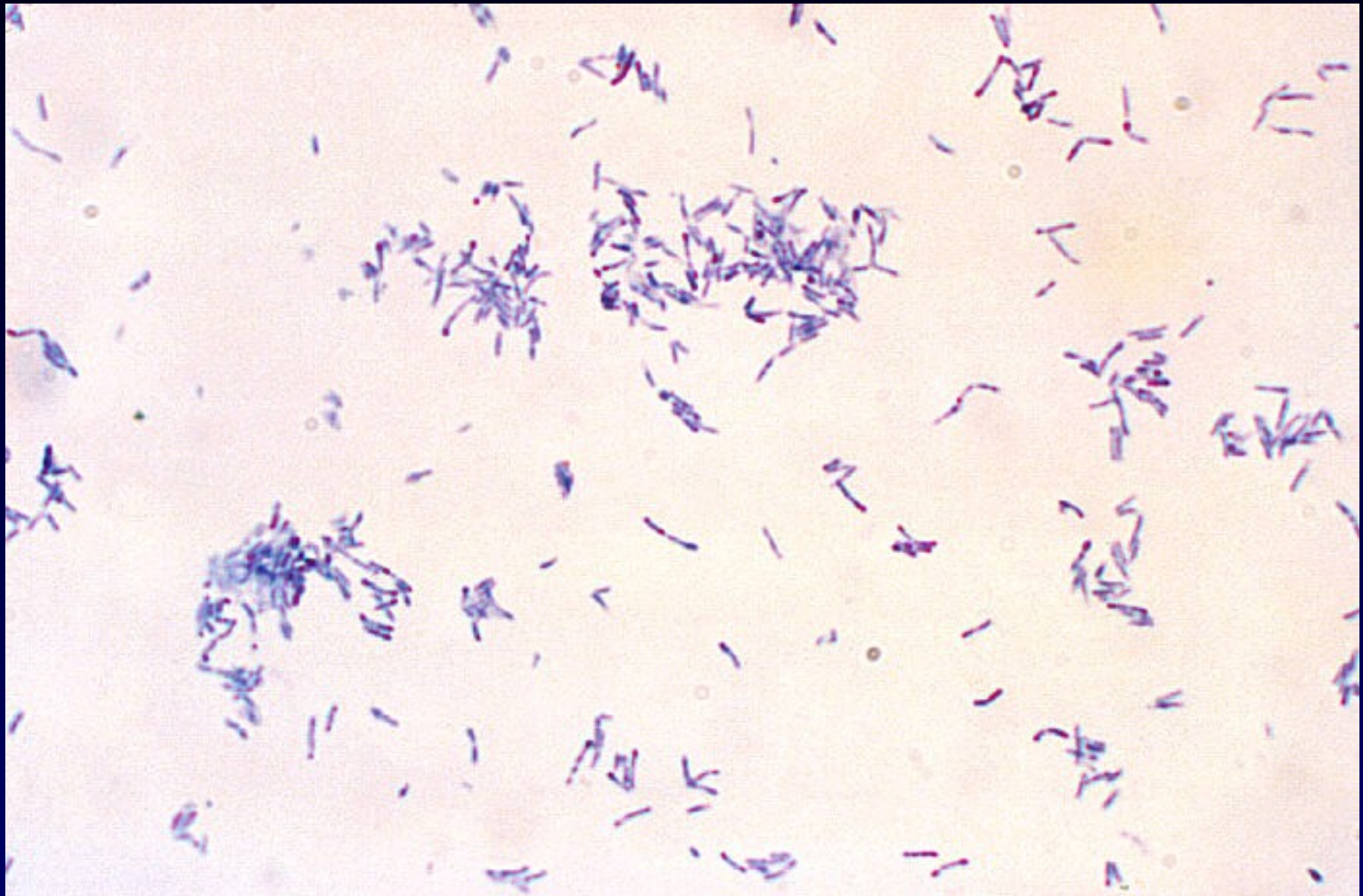
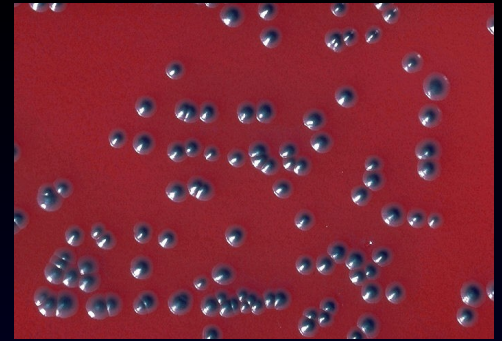


Diphtheria: Basic Characteristics

- *Corynebacterium diphtheriae*
 - Diphtherite (Greek) for hide or leather
- Pleomorphic gram + bacillus
- Curved or club-shaped



Diphtheria



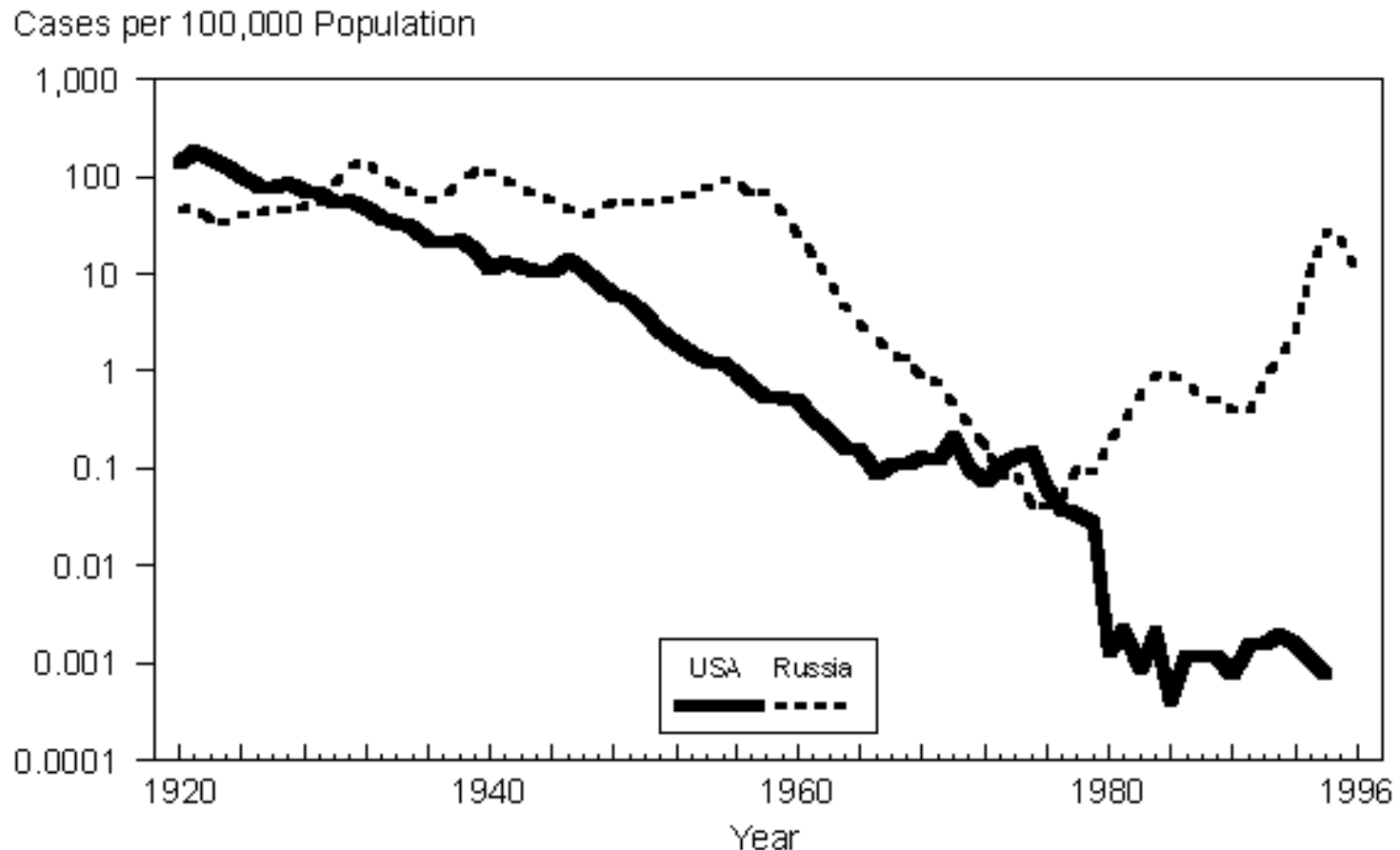
Diphtheria: Geographic Distribution

- Pre-vaccine
 - Highly endemic in temperate climates
 - One of leaders of childhood death
 - Affected elementary aged children
 - Fall peaks (? b/c of school)
 - Big epidemics every several years

Diphtheria: Geographic Distribution

- Post-Vaccine Era (1930's and '40's)
 - US, Canada, Western Europe
 - Almost eliminated
 - Resurgence in Germany/Europe in WW II
 - Today, some European countries haven't reported cases for 20 years
- Tropical Areas: not a big problem
 - Cutaneous infections hyperendemic

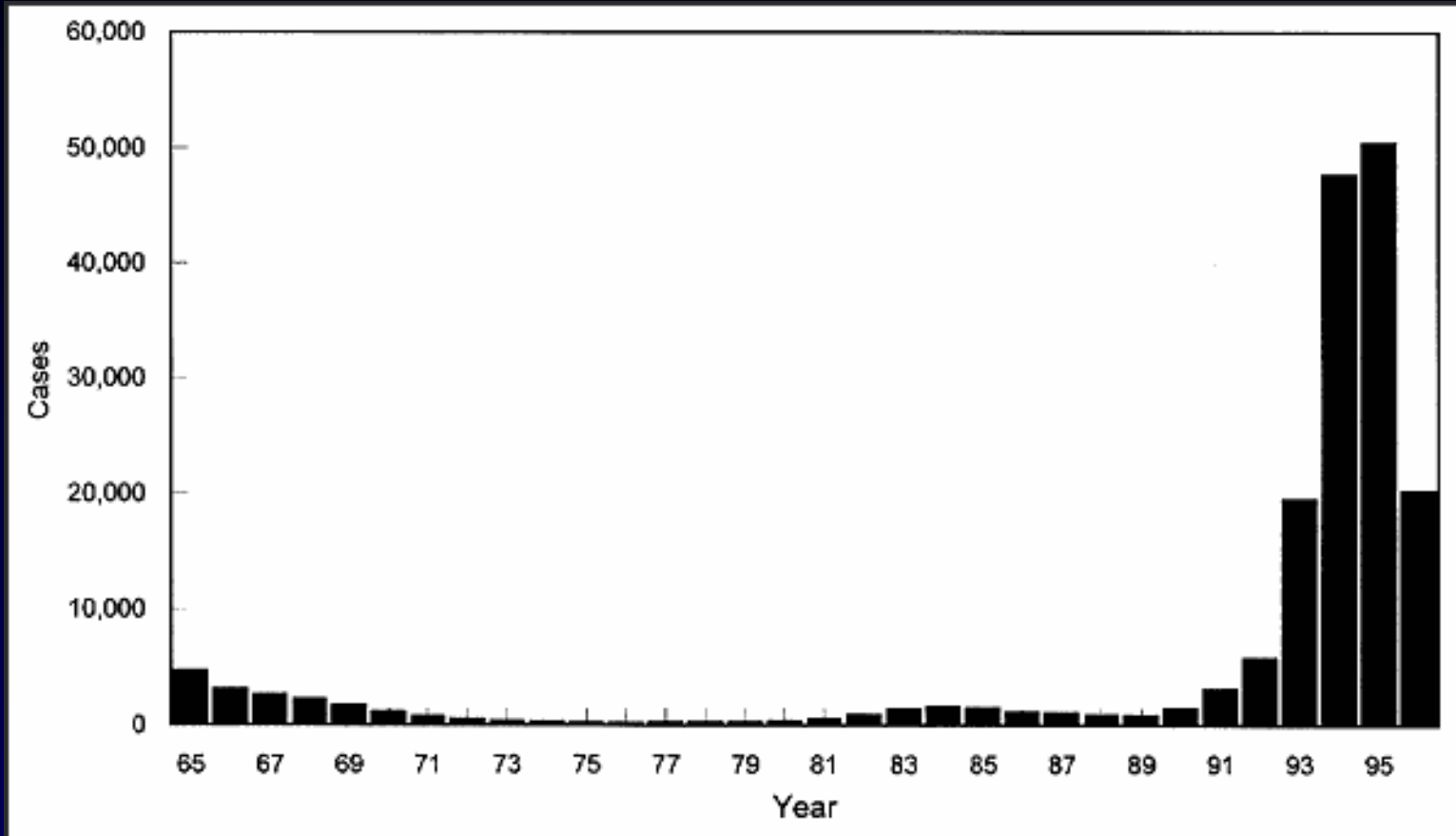
Diphtheria Incidence—United States and Russian Federation, 1920–1996.



Charles R. Vitek and Melinda Wharton. Diphtheria in the Former Soviet Union: Reemergence of a Pandemic Disease. EID 1998; 4(4): 539-50.

Diphtheria: Geographic Distribution

- Reemergence in former Soviet Union and newly independent states in 1990's



Charles R. Vitek and Melinda Wharton. Diphtheria in the Former Soviet Union: Reemergence of a Pandemic Disease. EID 1998; 4(4): 539-50.

Diphtheria: Mode of Transmission

- Humans only known hosts
- Contagious
 - Respiratory tract droplets
 - Contact with lesions
 - Fomites: dust for up to 3-6 months
 - Respiratory and contact precautions
 - Incubation: 2-4 days but up to 7



Diphtheria: Signs and Symptoms

- Primary Infections
 - Respiratory Disease
 - Cutaneous Disease
- Secondary sites from toxin
 - Cardiac Disease
 - Neurological disease

Diphtheria: Signs and Symptoms

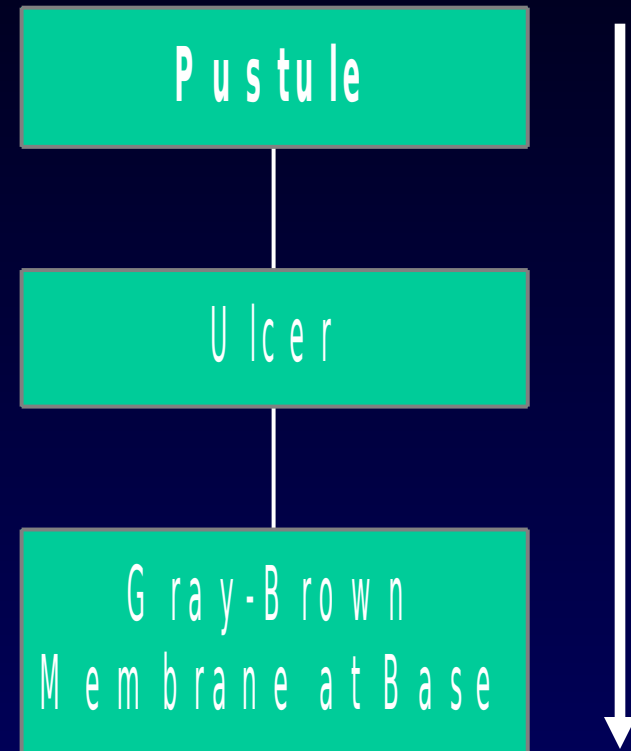
- Respiratory Diphtheria
 - Usually nasopharyngeal
 - Sore throat, malaise = most common
 - Characteristic membrane forms
 - Initially white and smooth → grey
 - Later patches of green and black = necrosis
 - Size dictates problems: can affect breathing
 - Cervical LAD and edema = bull neck

Diphtheria: Signs and Symptoms

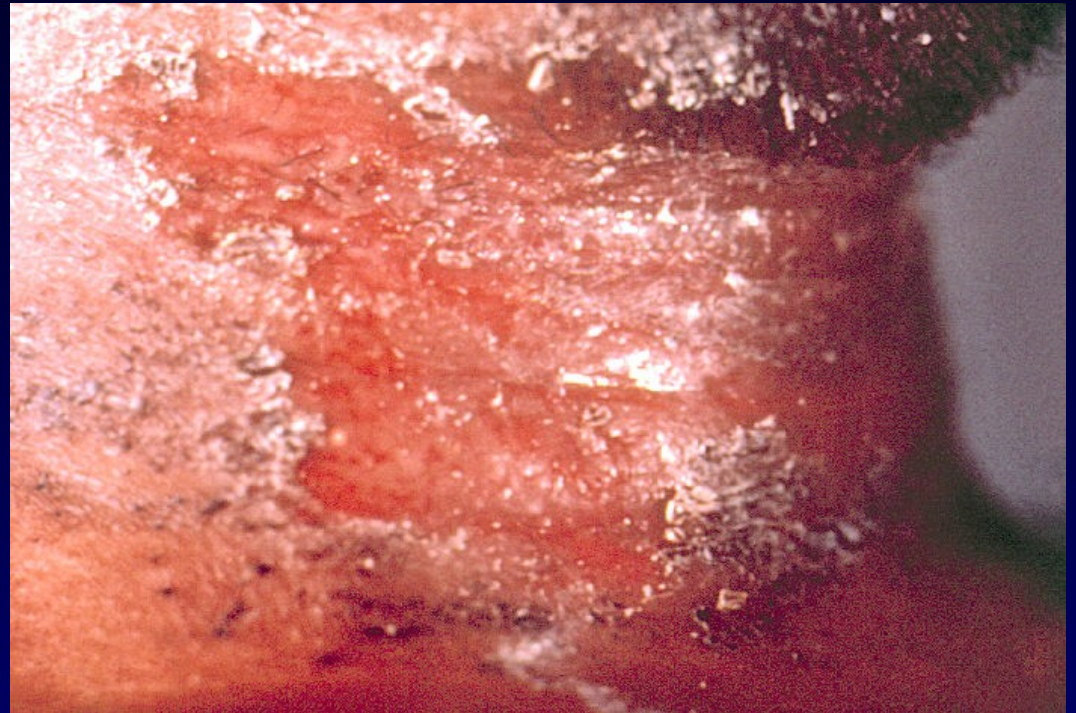
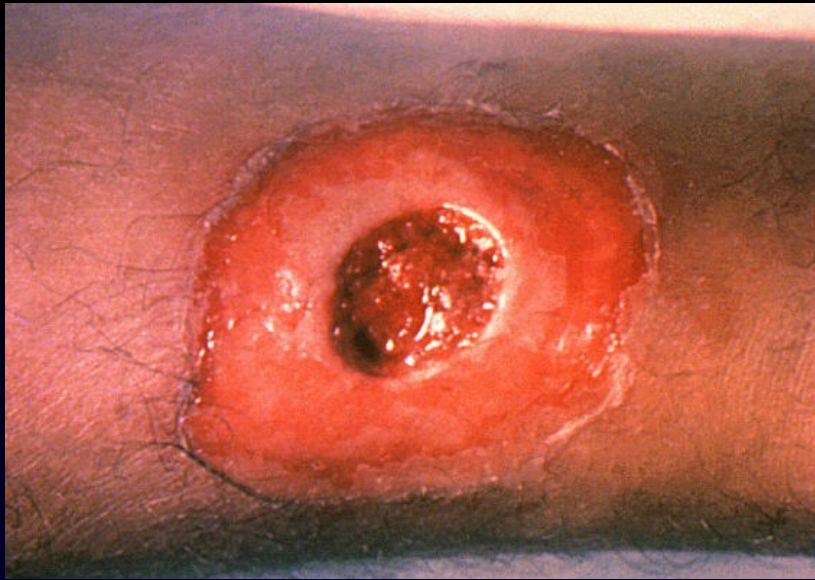


Diphtheria: Signs and Symptoms

- Cutaneous diphtheria
 - Superinfects old wounds
 - Can be primary infx
 - High levels of immunity to prevent systemic symptoms
 - Higher risk of transmission



Cutaneous Diphtheria



Signs and Symptoms

- Cardiac Disease
 - Myocarditis with significant dysfunction
 - 10-20% of pts severity correlates
 - ST-segment and T-wave abnl; LBBB, AV block
 - Injury can be permanent if survived
 - Decrease incidence with tx within 4 days
- Neurologic Disease
 - 10% all pts; 75% with severe disease
 - Severity correlates with respiratory dz
 - Cranial Nerves (IX, X early; other 2-5 wks later)
 - Peripheral Neuropathy (primarily motor)
 - Can occur in absence of CNS lesions

Diphtheria: Complications

- Airway Obstruction
 - Extension of membrane into larynx
 - 4-15% of respiratory cases
 - Fatal in 40-100%
 - Prevent: early intubation
- Pneumonia: 2-7%
 - Rarely from diphtheria
 - Aspiration, post-obstruction

Diphtheria Diagnosis: Clinical

- Pharyngeal disease with cardiac +/- neurological abnormalities
- Pseudomembrane
 - Rubs off easily, but bleeds underneath
- Few causes of “bull neck”
 - Ludwig’s angina
 - Subcutaneous air



Diphtheria Diagnosis: Laboratory

- Culture on selective media
 - Tellurite media (Tinsdale), blood agar, Loeffler slant incubated at 35-37 degrees
 - Gram stain can be helpful early
 - Sample sources
 - Nasal and pharyngeal swabs (under membrane)
 - Deep samples from skin (not surface swabs)
- Toxin Production
 - Multiple approaches

Diphtheria: Treatment

- Hospitalize all patients if possible
- Contact and droplet precautions
 - Maintain until 2 negative cultures
- Antitoxin
 - Most effective the earlier given
 - Not effective if given after 4 days of illness
 - Equine hyper-immune serum
 - Scratch test on forearm with 1:100 dilution
- Antibiotics
 - 2 week course

Diphtheria: Treatment

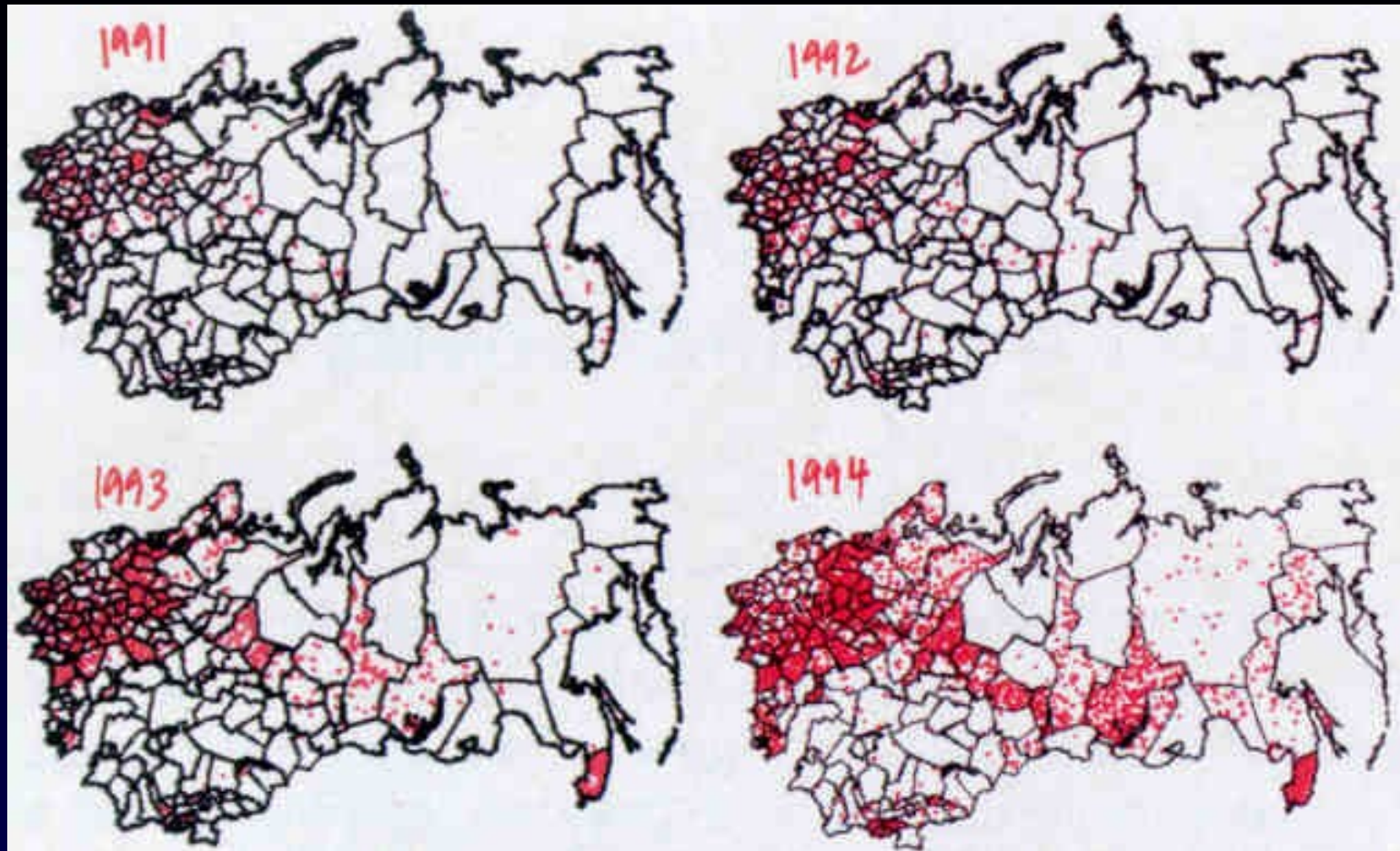
- Antitoxin
 - Available from CDC (404) 639-8200
 - Pharynx / Larynx: 20K-40K U IV
 - Nasopharynx: 40-60K U IV
 - Extensive dz or sx > 3d: 80K-120K U IV
- Erythromycin
 - 40-50mg/kg/d (max 2g/d) divided in 4 doses
- Alternate = PCN
 - Pen G 100K-150K U/kg/d divided q6H (max 12-20 mil)
 - Procaine PCN 25K-50K U/kg/d divided q12 (max 1.2 mil)

Diphtheria: Prevention

- Vaccine Preventable Disease, Toxoid
 - Full strength=D (DTaP); 1/5 strength=d (Td)
 - Booster
 - DTaP at school entry, especially if started at <4 weeks old
 - Adults: every 10 years (d)
 - Global diphtheria decreased by 70% from mid 1970's to early 1990's
- Prophylaxis of close contacts
 - Oral emycin (same as IV dose) X 1 week
 - Single IM benzathine Pen G
 - 600K U if <30 kg; 1.2 mil U if >30 kg

Diphtheria: Mission Impact

- Epidemic outbreak in former Soviet Union shows what happens when prevention measures are lifted and a vulnerable population is at risk.



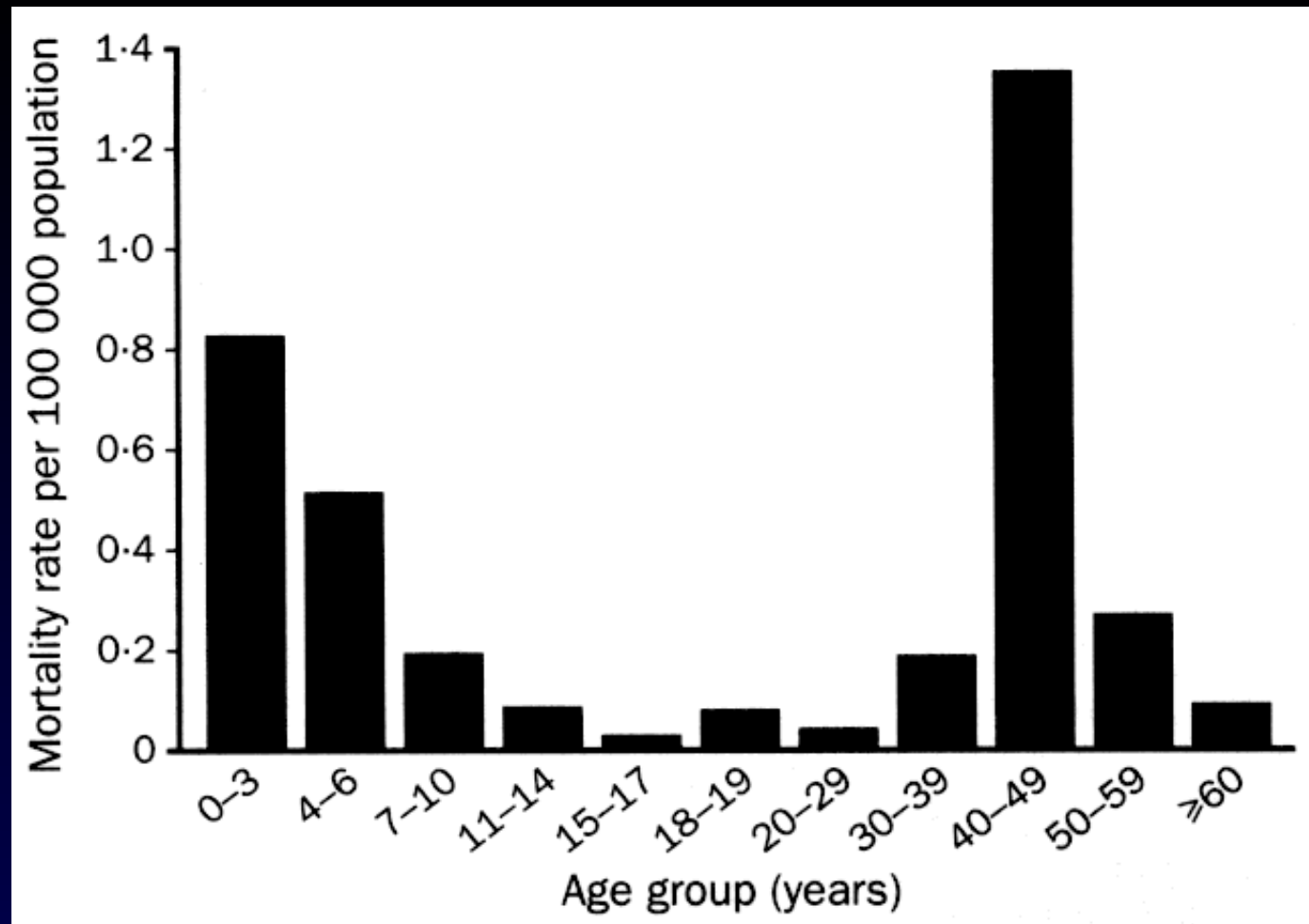
**Evolution of diphtheria epidemic in
former Soviet Union, 1991-94 One
dot=ten cases.**

Hardy: Lancet, Volume 347(9017).June 22, 1996.1739-1744

Diphtheria: Mission Impact

- Former Soviet Union
 - Peak = 50,412 cases (39,582 in Rus Fed)
 - Rus Fed 1993: 2/3 of cases > 14 y.o.
 - Persons 40-49 y.o.
 - 45% of all deaths = highest rate (1.3/100K)

Vitek CR and Wharton M. Diphtheria in the former Soviet Union: reemergence of a pandemic disease. EID 1993; 4(4):539-50.



Age-specific diphtheria incidence and mortality rates, Russian Federation, 1993.

Hardy: Lancet, Volume 347(9017).June 22, 1996.1739-1744

Diphtheria: Mission Impact

- Former Soviet Union: What Went Wrong?
 - Susceptible adult population
 - Susceptible population of children
 - New clone introduced into area
 - Crowding in urban areas
 - Disruption in vaccine supply after break-up
 - Breakdown in public health systems

Diphtheria: Mission Impact

- Lessons learned
 - Vaccination effort controlled epidemic
 - National (Russian Federation) and International (for Independent States) came together to battle epidemic
 - Archetype for increased susceptibility in adults to childhood diseases with successful childhood vaccine campaigns?

Diphtheria: Summary

- Distribution: sporadic cases but recent outbreak in former Soviet Union and Independent States
- Clinical Disease
 - Nasopharyngeal: pseudomembrane, bull neck
- Treatment: Antitoxin + Abx (Emycin > PCN)
- Diagnosis: Clinical, Culture and show toxin
- Prevention: Vaccination, Abx (Emycin, PCN)
- Mission Impact:
 - Devastating disease in susceptible population
 - Vaccination + abx aborted recent epidemic

Case Report



Meningococemia: Basic Characteristics

- *Neisseria meningitidis*
- Aerobic gram-negative diplococcus
- Serogroups based on polysaccharide capsule of cell wall
 - A, B, C, Y, and W-135 most common
 - Each serogroup has multiple serotypes



Photo: UT Houston Medical School Website

Meningococccemia: Basic Characteristics

- Humans are only reservoir
- Fulminant disease
- High mortality – not improved for 50 yrs
- Targets adolescents

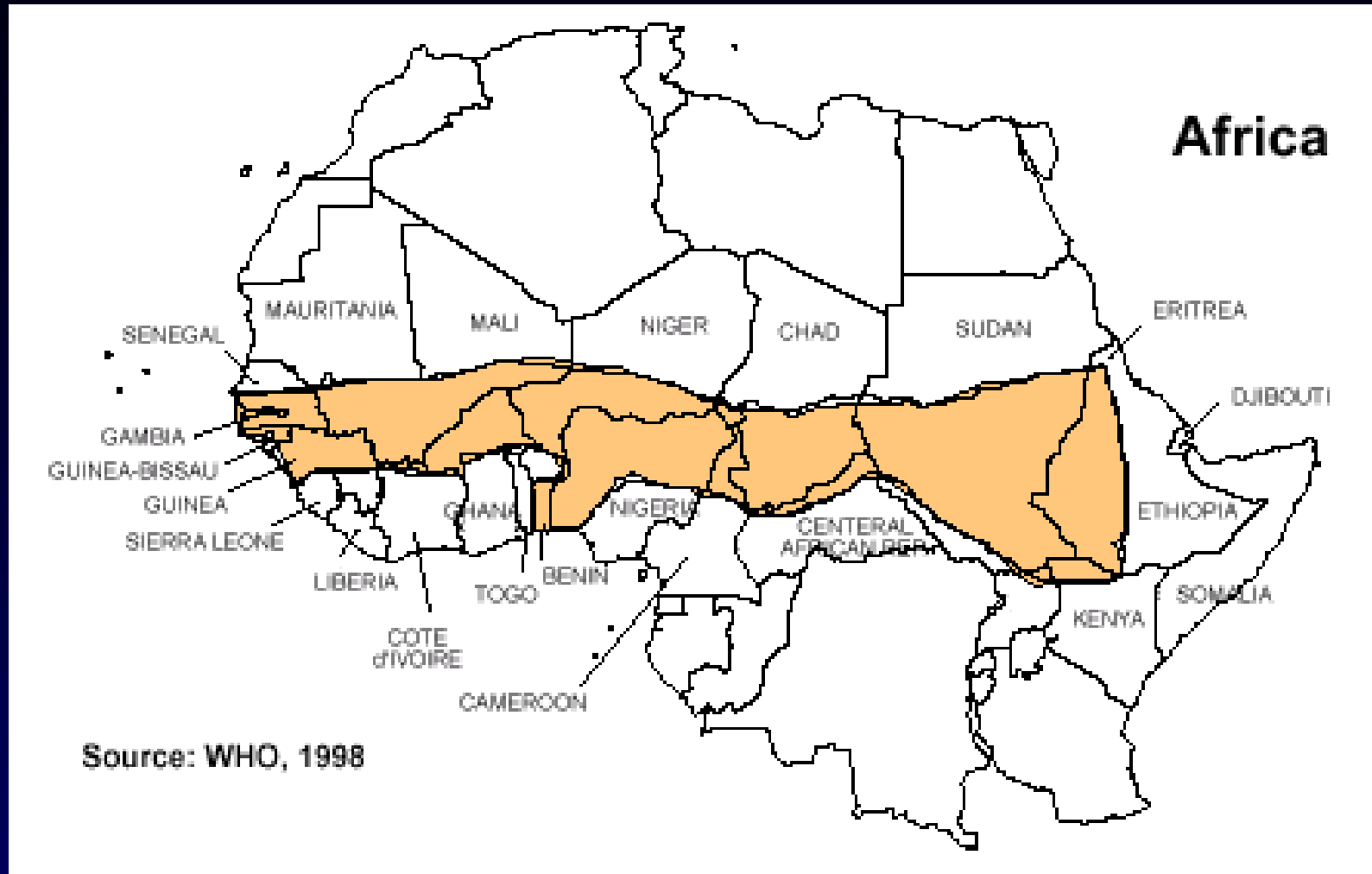
Meningococcus: Geographic Distribution

- Industrialized nations
 - Localized outbreaks causing high alarm
 - 50% B group (endemic), 20% C (epidemic)
 - 1-2 per 100,000 per year

Meningococcus: Geographic Distribution

- Sub-Saharan Africa = “meningitis belt”
 - Baseline rate = 10-25 per 100,000 per year
 - Group A (some C) strains cause epidemics every 8-12 years
- Asia: regularly occurs in Mongolia
- Indian Subcontinent
 - Outbreaks in Afghanistan, India, Nepal
- Mecca, Saudi Arabia, during the Hajj

Map: Areas with Frequent Epidemics of Meningococcal Meningitis, 2000



Health Information for International Travel, 2001–2002,
CDC

Meningococcus: Mode of Transmission

- Respiratory droplets from carriers
- Carrier rates
 - 95% in group A epidemics
 - 50% in military recruits
 - 10-15% general US population
 - Rates increase with crowding (prison, refugees, college dorms)
- Highest attack rates in Winter and Spring

Ferguson et al. N. meningitidis: presentation, treatment, and prevention. J pediatr Health Care 2002; 16:119-24

Meningococcus: Signs and Symptoms

- Acute bacterial meningitis
 - Headache, nausea, vomiting, meningismus
 - Rapidly progressive
 - Pharyngitis usually precedes meningitis
 - Chills, malaise common
 - High fever is norm – no fever is poor prognostic sign

Meningococcus: Signs and Symptoms



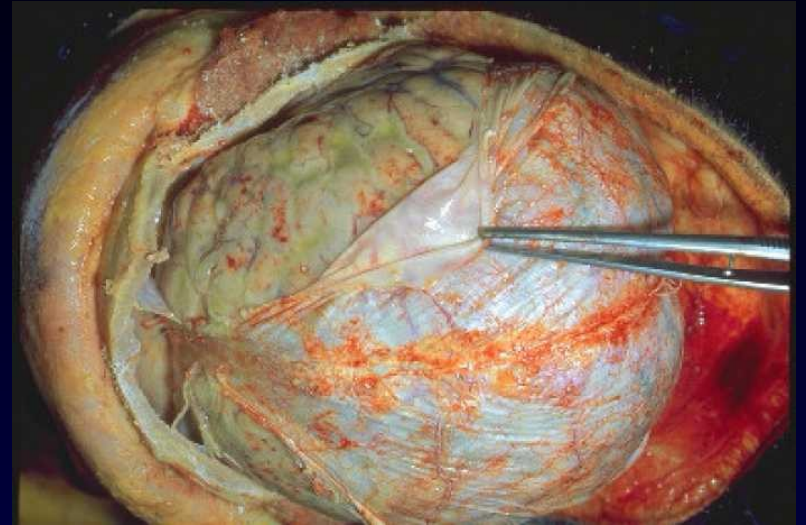
- Petechial rash
 - Starts distally and spreads to trunk
 - Palms and soles involved commonly
 - develops over hours to days

Meningococcus: Signs and Symptoms

- Acute meningococemia without meningitis
 - Presents as gram negative sepsis
 - Higher M and m due to rapid progression
- Waterhouse-Friederichsen syndrome
 - Fulminant meningococemia
 - Vascular collapse develops over hours
 - Occurs in 5-15% of meningitis cases
 - Preceded by restlessness, MS changes
 - Hallmark: adrenal infarction
- Chronic meningitis
 - Rare more indolent disease

Meningococcus: M and m

- Pneumonia
 - 15-20% of cases
 - May occur alone
- DIC
- Adrenal hemorrhage
- Distal necrosis / gangrene
- Mortality
 - 50% historically
 - 5-15% with modern dx and tx
 - Varies by SES
 - Cause: circulatory collapse
 - Occurs early in disease



Meningococcus

Diagnosis: Clinical

- Fulminant bacterial meningitis
- Characteristic petechial rash
 - Extremities to trunk



Meningococcus

Diagnosis: Laboratory

- Culture organism
 - CSF, blood, throat swab, skin lesions
 - Much higher yield if pre-abx
 - Blood Cx + 50% pre vs 5% post
 - Skin lesions GS + in 70%
- CSF: classic for bacterial meningitis
 - PMN predominance, low glucose, normal to high protein
 - Gram stain + in 70%
- Fastidious: plated on chocolate agar ASAP

Meningococcus:

Differential Diagnosis

- Rickettsial diseases
- Toxic shock syndrome
- Vasculitis
- Viral illness



Meningococcus: Treatment

	Adults	Children
1st Choice	Pen G 2.4 mil U IV Divided q2-4 H	Pen G 0.25 mil U/kg/d IV Divided q2-4 H
Alternative	Ceftriaxone 2g IV q12 Chlor 50-100mg/kg/d IV or PO q6H	Ceft 80-100mg/kg/d IV q12 Chlor - same as adults

Treat for 4-10 days

Wilson. Current diagnosis and treatment in infectious diseases.
2001. pp546

Meningococcus: Prevention

- Vaccine
 - Quadrivalent (A, C, Y, W-135)
 - 0.5 ml SC X 1 (repeat if < 4 y.o)
- History
 - Approved 1960's in US (A and C)
 - 1971 – all recruits received C vaccine
 - 1982 – A, C, Y, W-135 US Military
- Why no B vaccine? – not immunogenic
- Polysaccharide vaccines not effective in infants < 3 y.o.
 - A may have some efficacy at 2 months
- Future: conjugate vaccines

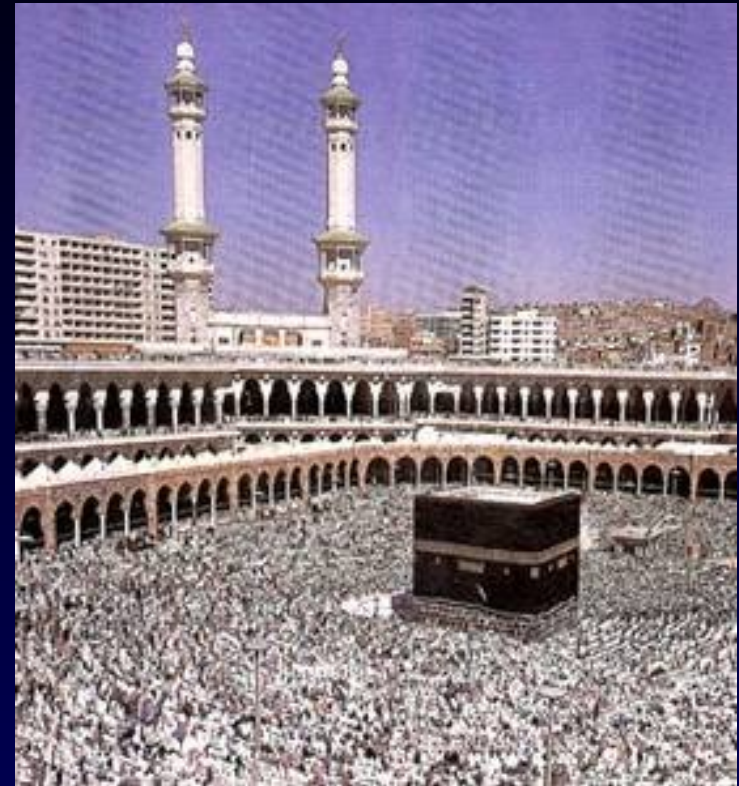
Meningococcus: Prevention

- Droplet precautions until 24H on tx
- Prophylaxis of contacts
 - Rifampin 10mg/kg (max 600mg) po q12-24H X 4 doses
 - Cipro 500 or 750mg po X 1 dose
 - Azithromycin 500mg X 1
 - Ceftriaxone 250mg IM X 1 (125 for kids)
- Accepted definition of “close contacts”:

Close contact of at least 4 hours during week preceding illness (ie: household or prison) or exposure to pts nasopharyngeal secretions (ie: kissing, mouth-to-mouth, intubation, suctioning)*

Meningococcus: Prevention

- Rec for college students (dorms)
 - Not covered by HMO's (\$70)
- Travelers to meningitis belt of Africa during the dry season
- REQUIRED for all going to Mecca, Saudi Arabia during Hajj
- Any traveler to country experiencing an outbreak
- Asplenic, terminal complement deficiency
- Duration of immunity: 3-4 years
 - Need booster



**Mecca, Saudi Arabia
during annual Hajj**

Meningococcus: Mission Impact

- Sporadic cases and outbreaks can occur throughout the world
- Consider in missions with proximity to large numbers of children
- High risk in sub-Saharan Africa
- Vaccine preventable disease

Meningococcus: Summary

- Distribution: epidemics in sub-Saharan Africa
- Clinical Disease
 - Fulminant meningitis, shock, DIC, petechial rash
- Treatment: PCN > Ceftriaxone > Chloramphen
- Diagnosis: Clinical, Culture in lab
- Prevention: Vaccine, Abx (Rifampin, Cipro, Ctx)
- Mission Impact:
 - Vaccine and abx can abort outbreaks
 - Protect yourself before missions